

Application No. 10/518,817
 Amendment Dated December 1, 2005
 Reply to Office Action of September 26, 2005

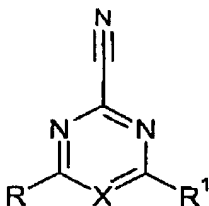
AstraZeneca Docket No. 100727-1P US

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1. (currently amended) A method of ~~inhibiting cathepsin S in a mammal~~ comprising administering a compound of formula (I) to ~~a~~ said mammal



(I)

in which:

X is N- or CA where A is hydrogen, halogen, CHR^2R^3 , OR^2 , NR^2R^3 , or SR^2 ;

R^2 and R^3 are independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl both of which can optionally contain one or more O, S or NR^4 groups where R^4 is hydrogen or C_{1-6} alkyl, and can be optionally substituted by aryl, heteroaryl, NR^5R^6 where R^5 and R^6 together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR^4 , or R2 and R3 together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR^4 group, or R2 and R3 are aryl or heteroaryl groups, both aryl and heteroaryl groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR^7R^8 , $\text{SO}_2\text{NR}^7\text{R}^8$, SO_2R^4 , trifluoromethyl, NHSO_2R^4 , NHCOR^4 , ethylenedioxy, methylenedioxy, C_{1-6} alkyl, C_{1-6} alkoxy, NR^7R^8 or SR^7 where R^7 and R^8 are independently hydrogen or C_{1-6} alkyl;

R and R^1 are independently a group $\text{Y}(\text{CH}_2)_p\text{R}^{10}$ where p is 0, 1, 2 or 3 and Y is O or NR^{10} where R^{10} is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

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and R^9 is hydrogen, C_{1-6} alkyl which can optionally contain one or more O, S or NR^4 groups where R^4 is hydrogen or C_{1-6} alkyl, or a 3 to 7-membered saturated ring optionally containing a carbonyl group, one or more O, S or N atoms, or an aryl or heteroaryl group containing one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, $CONR^7R^8$, $SO_2NR^7R^8$, SO_2R^4 , trifluoromethyl, $NHSO_2R^4$, $NHCOR^4$, ethylenedioxy, methylenedioxy, C_{1-6} alkyl, C_{1-6} alkoxy, SR^5 or $NR^{11}R^{12}$ where R^{11} and R^{12} are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^4 group; or R/R^1 is a group $NR^{10}(CHR^{10})CONR^2R^3$ or $NR^{10}(CH_2)_qCONR^2R^3$ where q is 1, 2 or 3; or R/R^1 is a group $NR^{13}R^{14}$ where R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by C_{1-6} alkyl, amino, hydroxy, CO_2C_{1-6} alkyl, halogen, NR^5R^6 , NR^7R^8 , C_{1-6} alkyl $NR^{17}R^{18}$ where R^{17} and R^{18} are independently hydrogen or C_{1-6} alkyl, $CONR^{15}R^{16}$ where R^{15} and R^{16} are independently hydrogen or C_{1-6} alkyl, or optionally substituted by aryl, phenoxy, CO phenyl, or a heteroaryl group, the latter four groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, $CONR^7R^8$, $SO_2NR^7R^8$, SO_2R^4 , trifluoromethyl, $NHSO_2R^4$, $NHCOR^4$, ethylenedioxy, methylenedioxy, C_{1-6} alkyl, C_{1-6} alkoxy, SR^5 or $NR^{11}R^{12}$ where R^{11} and R^{12} are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^4 group;

~~and/or a pharmaceutically acceptable salt or solvates thereof, in the manufacture of a medicament for use in the inhibition of cathepsin S in a mammal such as man.~~

Claim 2. (currently amended) The method according to claim 1 in which ~~X-A~~ is CH, NHR^2 , or OR^2 wherein R^2 is hydrogen or C_{1-6} alkyl.

Claim 3. (previously presented) The method according to claim 1 In which R is a group $Y(CH_2)_pR^7$ where p is 0 or 1 and Y is NR^8 wherein R^8 is hydrogen and R^7 is substituted phenyl.

Claim 4. (previously presented) The method according to claim 1 In which R^1 is a group $NR^{13}R^{14}$ where R^{13} and R^{14} together with the nitrogen atom to which they are attached form a morpholine ring, piperidine or piperazine ring optionally substituted.

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Claim 5. (previously presented) The method according to claim 1 in which R¹ is a group NR⁹R¹⁰ where R¹⁰ is H or C₁₋₆ alkyl and R⁹ is C₁₋₆ alkyl which can optionally contain one or more O, S or NR⁴ groups where R⁴ is hydrogen or C₁₋₆ alkyl.

Claim 6.(currently amended) The method according to claim 1 where the compound of formula (I) is selected from:

4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-1,3,5-triazine-2-carbonitrile,
4-Morpholin-4-yl-6-(4-phenoxy-piperidin-1-yl)-1,3,5-triazine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,
4-(7-Azabicyclo[2.2.1]hept-7-yl)-6-[(4-chlorophenyl)amino]-1,3,5-triazine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-yl-1,3,5-triazine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-piperidin-1-yl-1,3,5-triazine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-(ethylamino)-1,3,5-triazine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-(3-hydroxypyrrolidin-1-yl)-1,3,5-triazine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-[(2-piperidin-1-ylethyl)amino]-1,3,5-triazine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-(4-phenylpiperidin-1-yl)-1,3,5-triazine-2-carbonitrile,
4-[(3-Chlorobenzyl)amino]-6-(dimethylamino)-1,3,5-triazine-2-carbonitrile,
4-Morpholin-4-yl-6-[(4-morpholin-4-ylphenyl)amino]-1,3,5-triazine-2-carbonitrile,
4-(2,3-Dihydro-1,4-benzodioxin-6-ylamino)-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,
4-Morpholin-4-yl-6-(3-phenylpiperidin-1-yl)-1,3,5-triazine-2-carbonitrile,
4-(1,4'-Bipiperidin-1'-yl)-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,
4-[4-(1H-Imidazol-1-yl)piperidin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,
4-[4-(4-Chlorobenzoyl)piperidin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,
4-[4-(5-Chloropyridin-2-yl)piperazin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,
4-Morpholin-4-yl-6-[(3-(2-oxopyrrolidin-1-yl)propyl)amino]-1,3,5-triazine-2-carbonitrile,
1-(4-Cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N,N-diethylpiperidine-3-carboxamide,
4-[4-(2-Methoxyphenyl)piperazin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,
N-2-[(4-Cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N-1-yl]-N-1-bis[4-[N-(4-cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N-isobutylglycyl]morpholin-3-yl]-N-2-isobutylglycinamide,
4-Morpholin-4-yl-6-[(2-pyridin-3-ylethyl)amino]-1,3,5-triazine-2-carbonitrile,
4-[(2-(2-Furyl)ethyl)amino]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-(4-methylpiperazin-1-yl)-1,3,5-triazine-2-carbonitrile,
4-Azetidin-1-yl-6-[(4-chlorophenyl)amino]-1,3,5-triazine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,

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4-[(4-Methylcyclohexyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-(4-Chlorophenoxy)-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-(dimethylamino)pyrimidine-2-carbonitrile,
4-[(1-Methylpiperidin-4-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-(Cyclohexylamino)-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-ylpyrimidine-2-carbonitrile,
4-[(6-Chloropyridin-3-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,
1-[6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl]-L-prolinamide,
4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]pyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-(4-pyrrolidin-1-ylpiperidin-1-yl)pyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidine-2-carbonitrile,
tert-Butyl 4-[6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl]piperazine-1-carboxylate,
4-[(4-Chlorophenyl)amino]-6-(cyclopropylamino)pyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-piperazin-1-ylpyrimidine-2-carbonitrile,
(2S)-N~2~-{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-N~1~,N~1~-bis[4-(N-{6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-leucyl)morpholin-3-yl]-L-leucinamide,
5-Chloro-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-5-methoxy-6-piperazin-1-ylpyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-5-methoxy-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-[(3S)-3-Aminopyrrolidin-1-yl]-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-{4-[3-(dimethylamino)propyl]piperazin-1-yl}-5-methoxypyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-5-methoxypyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-5-methoxy-6-(3-oxopiperazin-1-yl)pyrimidine-2-carbonitrile,
1-[6-[(4-Chlorophenyl)amino]-2-cyano-5-methoxypyrimidin-4-yl]piperidine-3-carboxamide,
4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-carbonitrile,
5-Amino-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile, and
5-Amino-4-[(4-Chlorophenyl)amino]-6-(ethylamino)pyrimidine-2-carbonitrile, and pharmaceutically acceptable salts thereof.

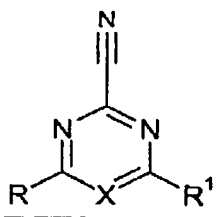
Claim 7. (cancelled)

Claim 8. (cancelled).

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Claim 9. (currently amended) A pharmaceutical composition which comprises a compound of formula (I):



(I)

in which:

X is CA where A is hydrogen, halogen, CHR^2R^3 , OR^2 , NR^2R^3 , or SR^2 ;

R^2 and R^3 are independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl both of which can optionally contain one or more O, S or NR^4 groups where R^4 is hydrogen or C_{1-6} alkyl, and can be optionally substituted by aryl, heteroaryl, NR^5R^6 where R^5 and R^6 together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR^4 , or R2 and R3 together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR^4 group, or R2 and R3 are aryl or heteroaryl groups, both aryl and heteroaryl groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR^7R^8 , $\text{SO}_2\text{NR}^7\text{R}^8$, SO_2R^4 , trifluoromethyl, NHSO_2R^4 , NHCOR^4 , ethylenedioxy, methylenedioxy, C_{1-6} alkyl, C_{1-6} alkoxy, NR^7R^8 or SR^7 where R^7 and R^8 are independently hydrogen or C_{1-6} alkyl;

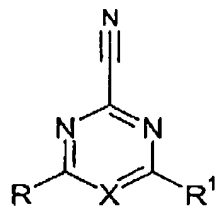
R and R^1 are independently a group $\text{Y}(\text{CH}_2)_p\text{R}^9$ where p is 0, 1, 2 or 3 and Y is O or NR^{10} where R^{10} is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;
and R^9 is hydrogen, C_{1-6} alkyl which can optionally contain one or more O, S or NR^4 groups where R^4 is hydrogen or C_{1-6} alkyl, or a 3 to 7-membered saturated ring optionally containing a carbonyl group, one or more O, S or N atoms, or an aryl or heteroaryl group containing one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR^7R^8 , $\text{SO}_2\text{NR}^7\text{R}^8$, SO_2R^4 , trifluoromethyl, NHSO_2R^4 , NHCOR^4 , ethylenedioxy,

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methylenedioxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, SR⁵ or NR¹¹R¹² where R¹¹ and R¹² are independently hydrogen, C₁₋₆ alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR⁴ group;
or R/R¹ is a group NR¹⁰(CHR¹⁰) CONR²R³ or NR¹⁰(CH₂)_qCONR²R³ where q is 1, 2 or 3;
or R/R¹ is a group NR¹³R¹⁴ where R¹³ and R¹⁴ together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by C₁₋₆ alkyl, amino, hydroxy, CO₂C₁₋₆ alkyl, halogen, NR⁵R⁶, NR⁷R⁸, C₁₋₆ alkylNR¹⁷R¹⁸ where R¹⁷ and R¹⁸ are independently hydrogen or C₁₋₆ alkyl, CONR¹⁵R¹⁶ where R¹⁵ and R¹⁶ are independently hydrogen or C₁₋₆ alkyl, or optionally substituted by aryl, phenoxy, C₆H₄, or a heteroaryl group, the latter four groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR⁷R⁸, SO₂NR⁷R⁸, SO₂R⁴, trifluoromethyl, NHCO₂R⁴, NHCOR⁴, ethylenedioxy, methylenedioxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, SR⁵ or NR¹¹R¹² where R¹¹ and R¹² are independently hydrogen, C₁₋₆ alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR⁴ group,
a compound of the formula (I) as defined in claim 7 or a pharmaceutically acceptable salt thereof;
 and a pharmaceutically acceptable diluent or carrier.

Claim 10. (currently amended) A method ~~for producing inhibition of a cysteine-~~
~~protease in a mammal, such as man, in need of such treatment, which~~
~~comprises~~comprising:
 -administering to said ~~a~~ mammal an effective amount of a compound of formula (I);



(I)

in which;

X is CA where A is hydrogen, halogen, CHR²R³, OR², NR²R³, or SR²;

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R² and R³ are independently hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl both of which can optionally contain one or more O, S or NR⁴ groups where R⁴ is hydrogen or C₁₋₆ alkyl, and can be optionally substituted by aryl, heteroaryl, NR⁵R⁶ where R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR⁴, or R² and R³ together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR⁴ group, or R² and R³ are aryl or heteroaryl groups, both aryl and heteroaryl groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR⁷R⁸, SO₂NR⁷R⁸, SO₂R⁴, trifluoromethyl, NHSO₂R⁴, NHCOR⁴, ethylenedioxy, methylenedioxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, NR⁷R⁸ or SR⁷ where R⁷ and R⁸ are independently hydrogen or C₁₋₆ alkyl;

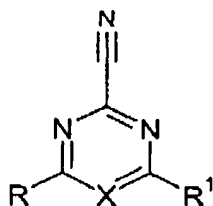
R and R¹ are independently a group Y(CH₂)_pR⁹ where p is 0, 1, 2 or 3 and Y is O or NR¹⁰ where R¹⁰ is hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl;
and R⁹ is hydrogen, C₁₋₆ alkyl which can optionally contain one or more O, S or NR⁴ groups where R⁴ is hydrogen or C₁₋₆ alkyl, or a 3 to 7-membered saturated ring optionally containing a carbonyl group, one or more O, S or N atoms, or an aryl or heteroaryl group containing one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR⁷R⁸, SO₂NR⁷R⁸, SO₂R⁴, trifluoromethyl, NHSO₂R⁴, NHCOR⁴, ethylenedioxy, methylenedioxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, SR⁵ or NR¹¹R¹² where R¹¹ and R¹² are independently hydrogen, C₁₋₆ alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR⁴ group;
or R/R¹ is a group NR¹⁰(CHR¹⁰) CONR²R³ or NR¹⁰(CH₂)_qCONR²R³ where q is 1, 2 or 3;
or R/R¹ is a group NR¹³R¹⁴ where R¹³ and R¹⁴ together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by C₁₋₆ alkyl, amino, hydroxy, CO₂C₁₋₆ alkyl, halogen, NR⁵R⁶, NR⁷R⁸, C₁₋₆ alkylNR¹⁷R¹⁸ where R¹⁷ and R¹⁸ are independently hydrogen or C₁₋₆ alkyl, CONR¹⁵R¹⁶ where R¹⁵ and R¹⁶ are independently hydrogen or C₁₋₆ alkyl, or optionally substituted by aryl, phenoxy, C₆H₄phenyl, or a heteroaryl group, the latter four groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR⁷R⁸, SO₂NR⁷R⁸, SO₂R⁴, trifluoromethyl, NHSO₂R⁴, NHCOR⁴, ethylenedioxy, methylenedioxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, SR⁵ or NR¹¹R¹² where R¹¹ and R¹² are independently hydrogen, C₁₋₆ alkyl or together with the nitrogen atom to which they are attached form a 5-

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~~or 6-membered saturated ring optionally containing a further O, S or NR⁴ groups compound of the present invention as defined in claim 7 or a pharmaceutically acceptable salt thereof.~~

Claim 11. (new) A method treating rheumatoid arthritis in a mammal comprising administering a compound of formula (I) to said mammal



(I)

in which:

X is CA where A is hydrogen, halogen, CHR²R³, OR², NR²R³, or SR²;

R² and R³ are independently hydrogen, C₁₋₆ alkyl or C₃₋₈ cycloalkyl both of which can optionally contain one or more O, S or NR⁴ groups where R⁴ is hydrogen or C₁₋₆ alkyl, and can be optionally substituted by aryl, heteroaryl, NR⁵R⁶ where R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR⁴, or R² and R³ together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR⁴ group, or R² and R³ are aryl or heteroaryl groups, both aryl and heteroaryl groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR⁷R⁸, SO₂NR⁷R⁸, SO₂R⁴, trifluoromethyl, NHSO₂R⁴, NHCOR⁴, ethylenedioxy, methylenedioxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, NR⁷R⁸ or SR⁷ where R⁷ and R⁸ are independently hydrogen or C₁₋₆ alkyl;

R and R¹ are independently a group Y(CH₂)_pR⁹ where p is 0, 1, 2 or 3 and Y is O or NR¹⁰ where R¹⁰ is hydrogen, C₁₋₆ alkyl or C₃₋₈ cycloalkyl;

and R⁹ is hydrogen, C₁₋₆ alkyl which can optionally contain one or more O, S or NR⁴ groups where R⁴ is hydrogen or C₁₋₆ alkyl, or a 3 to 7-membered saturated ring optionally containing a carbonyl group, one or more O, S or N atoms, or an aryl or heteroaryl group containing

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one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR^7R^8 , $\text{SO}_2\text{NR}^7\text{R}^8$, SO_2R^4 , trifluoromethyl, NHSO_2R^4 , NHCOR^4 , ethylenedioxy, methylenedioxy, C_{1-6} alkyl, C_{1-6} alkoxy, SR^5 or $\text{NR}^{11}\text{R}^{12}$ where R^{11} and R^{12} are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^4 group; or R/R^1 is a group $\text{NR}^{10}(\text{CHR}^{10})\text{CONR}^2\text{R}^3$ or $\text{NR}^{10}(\text{CH}_2)_q\text{CONR}^2\text{R}^3$ where q is 1, 2 or 3; or R/R^1 is a group $\text{NR}^{13}\text{R}^{14}$ where R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by C_{1-6} alkyl, amino, hydroxy, $\text{CO}_2\text{C}_{1-6}$ alkyl, halogen, NR^5R^6 , NR^7R^8 , C_{1-6} alkyl $\text{NR}^{17}\text{R}^{18}$ where R^{17} and R^{18} are independently hydrogen or C_{1-6} alkyl, $\text{CONR}^{15}\text{R}^{16}$ where R^{15} and R^{16} are independently hydrogen or C_{1-6} alkyl, or optionally substituted by aryl, phenoxy, COPhenyl , or a heteroaryl group, the latter four groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR^7R^8 , $\text{SO}_2\text{NR}^7\text{R}^8$, SO_2R^4 , trifluoromethyl, NHSO_2R^4 , NHCOR^4 , ethylenedioxy, methylenedioxy, C_{1-6} alkyl, C_{1-6} alkoxy, SR^5 or $\text{NR}^{11}\text{R}^{12}$ where R^{11} and R^{12} are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^4 group; or a pharmaceutically acceptable salt.

Claim 12. (new) The method according to claim 11 in which A is H, NHR^2 , or OR^2 wherein R^2 is hydrogen or C_{1-6} alkyl.

Claim 13. (new) The method according to claim 11 in which R is a group $\text{Y}(\text{CH}_2)_p\text{R}^7$ where p is 0 or 1 and Y is NR^8 wherein R^8 is hydrogen and R^7 is substituted phenyl.

Claim 14. (new) The method according to claim 11 in which R^1 is a group $\text{NR}^{13}\text{R}^{14}$ where R^{13} and R^{14} together with the nitrogen atom to which they are attached form a morpholine ring, piperidine or piperazine ring optionally substituted.

Claim 15. (new) The method according to claim 11 in which R^1 is a group NR^8R^{10} where R^{10} is H or C_{1-6} alkyl and R^8 is C_{1-6} alkyl which can optionally contain one or more O, S or NR^4 groups where R^4 is hydrogen or C_{1-6} alkyl.

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Reply to Office Action of September 26, 2005

AstraZeneca Docket No. 100727-1P US

Claim 16.(new) The method according to claim 11 where the compound of formula (I) is selected from:

4-[(4-Chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-[(4-Methylcyclohexyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-(4-Chlorophenoxy)-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-(dimethylamino)pyrimidine-2-carbonitrile,
4-[(1-Methylpiperidin-4-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-(Cyclohexylamino)-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-ylpyrimidine-2-carbonitrile,
4-[(6-Chloropyridin-3-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,
1-[6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl]-L-prolinamide,
4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]pyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-(4-pyrrolidin-1-ylpiperidin-1-yl)pyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidine-2-carbonitrile,
tert-Butyl 4-{6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}piperazine-1-carboxylate,
4-[(4-Chlorophenyl)amino]-6-(cyclopropylamino)pyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-piperazin-1-ylpyrimidine-2-carbonitrile,
(2S)-N~2~-{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-N~1~,N~1~-bis[4-(N-{6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-leucyl)morpholin-3-yl]-L-leucinamide,
5-Chloro-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-5-methoxy-6-piperazin-1-ylpyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-5-methoxy-6-morpholin-4-ylpyrimidine-2-carbonitrile,
4-[(3S)-3-Aminopyrrolidin-1-yl]-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-{4-[3-(dimethylamino)propyl]piperazin-1-yl}-5-methoxypyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-5-methoxypyrimidine-2-carbonitrile,
4-[(4-Chlorophenyl)amino]-5-methoxy-6-(3-oxopiperazin-1-yl)pyrimidine-2-carbonitrile,
1-{6-[(4-Chlorophenyl)amino]-2-cyano-5-methoxypyrimidin-4-yl}piperidine-3-carboxamide,
4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-carbonitrile,
5-Amino-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile, and
5-Amino-4-[(4-Chlorophenyl)amino]-6-(ethylamino)pyrimidine-2-carbonitrile.